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(71) Applicant *(for all designated States except US)*: EUROCELTIQUE S.A. [LU/LU]; 122, boulevard de la Petrusse, L-Luxembourg (LU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LESLIE, Stewart, Thomas [GB/GB]; 4 Babraham Road, Cambridge CB2 2RA (GB). KNOTT, Trevor, John [GB/GB]; 35 Larksway, Bishops Stortford, Hertfordshire CM23 4DG (GB). MOHAMMAD, Hassan [GB/GB]; 5 Lilac End, Haslingfield, Cambridge CB3 7LG (GB). PRATER, Derek, Allan [GB/GB]; 28 Pearson Close, Milton, Cambridge CB4 6YS (GB).

(74) Agent: LAMB, John, Baxter; Marks & Clerk, 57-60 Lincoln's Inn Fields, London WC2A 3LS (GB).

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(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING A FUSIBLE CARRIER AND METHOD FOR PRODUCING THE SAME

(57) Abstract

A process for the manufactaure of particles comprises mechanically working a mixture of a drug and a hydrophobic and/or hydrophilic fusible carrier in a high speed mixture so as to form agglomerates, breaking the agglomerates to give controlled release particles and optionally continuing the mechanical working with the optional addition of a low percentage of the carrier or diluent.

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PHARMACEUTICAL COMPOSITION CONTAINING A FUSIBLE CARRIER AND METHOD FOR PRODUCING THE SAME

The present invention relates generally to a method of manufacturing pharmaceutical dosage forms, for human or veterinary use, preferably sustained release particles, such particles having diameters ranging from 0.1 to 3.0mm. Such particles may contain analgesics, such as morphine, or other active ingredients. The present invention also relates to dosage forms obtained by processing of the aforesaid particles, such as tablets, suppositories or pessaries.

In our co-pending British Patent Application No. 9404928.5 we describe a process for the manufacture of particles, preferably sustained release particles, which comprises

(a) mechanically working in a high-shear mixer, a mixture of a particulate drug and a particulate, hydrophobic and/or hydrophilic fusible carrier or diluent having a melting point from 35 to 150°C and optionally a release control component comprising a water-soluble fusible material or a particulate, soluble or insoluble organic or inorganic material, at a speed and energy input which allows the carrier or diluent to melt or soften whereby it forms agglomerates;

(b) breaking down the agglomerates to give controlled release particles; and optionally

(c) continuing mechanically working optionally with the addition of a low percentage of the carrier or diluent; and optionally

(d) repeating steps (c) and possibly (b) one or more times.

We have now found that satisfactory results may also be obtained if, instead of classifying the agglomerated material in stage b) the material from stage a) is formed into extrudates of predetermined size, and in preferred embodiments, higher yields and/or higher drug loadings, and greater uniformity of size, than in the earlier process first mentioned above still with satisfactory controlled release properties may be achieved.

The present invention thus includes in one aspect a process for the manufacture of particles, preferably sustained release particles, which comprises:-

(a) mechanically working in a high-shear mixer, a mixture of a particulate drug and a particulate, hydrophobic and/or hydrophilic fusible carrier or diluent having a melting point from 35 to 150°C and optionally a release control component comprising a water soluble fusible material or a particulate, soluble or insoluble, organic or inorganic material, at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates; and then

(b) extruding the resulting material.

The extrusion may be carried out so as to form a rod like extrudate which may be cut or moulded to form unit dosage forms e.g. tablets or suppositories, directly.

Preferably the extrusion is through a plurality of orifices and the extrudate is formed into pieces. In more preferred embodiments the extrusion is through a plurality of small orifices e.g. about 0.25mm to 1.5mm e.g. 0.5mm or 1.0mm diameter and the extrudate is formed into short lengths of e.g. 0.5 to 1.5mm e.g. 1.0mm, suitably by cutting.

A preferred process according to the invention comprises the further steps,

(c) of continuing mechanically working the pieces formed from the extrudate, optionally with a further addition of a low percentage of the carrier or diluent; and

(d) optionally repeating step (c) and possibly (b) one or more e.g. up to five times.

Extrusion and forming into short lengths by cutting may be carried out using e.g. an Alexanderwerk, Caleva or Nica machine.

Extrusion operations are well known in the formulation field and are described, for example in Pharmaceutical Dosage Forms, Volume 2, Ed. Lieberman and Lachman, Marcel Dekker Inc, New York and Basel.

This process is capable of giving a high yield, generally greater than 85%, and preferably greater than 90% of particles in a desired size range, with a desired in vitro release rate and, uniformity of release rate.

The resulting particles may be sieved to eliminate any oversized or undersized material then formed into the desired dosage units by, for example, encapsulation into hard gelatin capsules containing the required dose of the active substance or by tabletting, filling into sachets or moulding into suppositories, pessaries or forming into other suitable dosage forms.

The drug may be water soluble or water insoluble. Water soluble drugs will usually be used in amounts giving for example a loading of up to about 90% w/w in the resulting particles; water insoluble drugs may be used in higher amounts eg. up to 99% w/w of the resulting particles; Examples of water soluble drugs which can be used in the method of the invention are morphine, hydromorphone, diltiazem, diamorphine and tramadol and pharmaceutically acceptable salts thereof; examples of water insoluble drugs which can be used in the process of the invention are naproxen, ibuprofen, indomethacin and nifedipine.

Among the active ingredient which can be used in the process of the invention are the following;

ANALGESICS and ANTIINFLAMMATORIES

Dihydrocodeine, Hydromorphone, Morphine, Diamorphine, Fentanyl, Alflentanil, Sufentanyl, Pentazocine, Buprenorphine, Nefopam, Dextropropoxyphene, Flupirtine, Tramadol, Oxycodone, Metamizol, Propyphenazone, Phenazone, Nifenazone, Paracetamol, Phenylbutazone, Oxyphenbutazone, Mofebutazone, Acetyl salicylic acid, Diflunisal, Flurbiprofen, Ibuprofen, Diclofenac, Ketoprofen, Indomethacin, Naproxen, Meptazinol, Methadone, Pethidine, Hydrocodone, Meloxicam, Fenbufen, Mefenamic acid, Piroxicam, Tenoxicam, Azapropazone, Codeine,

ANTIALLERGICS

Pheniramine, Dimethindene, Terfenadine, Astemizole, Tritoqualine, Loratadine, Doxylamine, Mequitazine, Dexchlorpheniramine, Triprolidine, Oxatomide,

ANTIHYPERTENSIVE

Clonidine, Moxonidine, Methyldopa, Doxazosin, Prazosin, Urapidil, Terazosin, Minoxidil, Dihydralazin, Deserpidine, Acebutalol, Alprenolol, Atenolol, Metoprolol, Bupranolol, Penbutolol, Propranolol, Esmolol, Bisoprolol, Ciliprolol, Sotalol, Metipranolol, Nadolol, Oxprenolol, Nifedipine, Nicadipine, Verapamil, Diltiazem, Felodipine, Nimodipine, Flunarizine, Quinapril, Lisinopril, Captopril, Ramipril, Fosinopril, Cilazapril, Enalapril,

ANTIBIOTICS

Democlocycline, Doxycycline, Lymecycline, Minocycline, Oxytetracycline, Tetracycline, Sulfametopyrazine, Ofloxacin, Ciproflaxacin, Aerosoxacin, Amoxycillin, Ampicillin, Becampicillin, Piperacillin, Pivampicillin, Cloxacillin, Penicillin V, Flucloxacillin, Erythromycin, Metronidazole, Clindamycin, Trimethoprim, Neomycin, Cefaclor, Cefadroxil, Cefixime, Cefpodoxime, Cefuroxine, Cephalexin, Cefradine.

BRONCHODILATOR/ANTI-ASTHMATIC

Pirbuterol, Orciprenaline, Terbutaline, Fenoterol, Clenbuterol, Salbutamol, Procaterol, Theophylline, Cholintheophyllinate, Theophylline-ethylenediamine, Ketofen,

ANTIARRHYTHMICS

Viquidil, Procainamide, Mexiletine, Tocainide, Propafenone, Ipratropium,

CENTRALLY ACTING SUBSTANCES

Amantadine, Levodopa, Biperiden, Benzotropine, Bromocriptine, Procyclidine, Moclobemide, Tranylcypromide, Clomipramine, Maprotiline, Doxepin, Opipramol, Amitriptyline, Desipramine, Imipramine, Fluroxamin, Fluoxetin, Paroxetine, Trazodone, Viloxazine, Fluphenazine, Perphenazine, Promethazine, Thioridazine, Triflupromazine, Prothipendyl, Tiotixene, Chlorprothixene, Haloperidol, Pipamperone, Pimozide, Sulpiride, Fenethylline, Methylphenildat, Trifluoperazine, Thioridazine, Oxazepam, Lorazepam, Bromoazepam, Alprazolam, Diazepam, Clobazam, Buspirone, Piracetam,

CYTOSTATICS AND METASTASIS INHIBITORS

Melfalan, Cyclophosphamide, Trofosfamide, Chlorambucil, Lomustine, Busulfan, Prednimustine, Fluorouracil, Methotrexate, Mercaptopurine, Thioguanin, Hydroxycarbamide, Altretamine, Procarbazine,

ANTI-MIGRAINE

Lisuride, Methysergide, Dihydroergotamine, Ergotamine, Pizotifen,

GASTROINTESTINAL

Cimetidine, Famotidine, Ranitidine, Roxatidine, Pirenzipine, Omeprazole, Misoprostol, Proglumide, Cisapride, Bromopride, Metoclopramide,

ORAL ANTIDIABETICS

Tobutamide, Glibenclamide, Glipizide, Gliquidone, Gliboruride, Tolazamide, Acarbose and the pharmaceutically active salts or esters of the above and combinations of two or more of the above or salts or esters thereof.

The hydrolysis of drugs constitutes the most frequent, and perhaps therefore the most important, route of drug decomposition. Analysis of a collection of stability data in Connors KA, Amidon GL, Stella VJ, Chemical stability of pharmaceuticals. A handbook for pharmacists, 2nd ed. New York: John Wiley & Sons, 1986, a standard text, shows that over 70% of the drugs studied undergo hydrolytic degradation reactions. Of these, 61.4% can be classed as reactions of carboxylic acid derivatives (esters, amides, thiol esters, lactams, imides), 20% of carbonyl derivatives (imines, oximes), 14.3% of nucleophilic displacements, and 4.3% of phosphoric acid derivatives. Cephalosporins, penicillins and barbituates are particularly susceptible drug classes.

The process of the invention may advantageously be used for preparing dosage forms containing active substances as mentioned above which are unstable in the presence of water, e.g. diamorphine. Thus stable formulations of such drugs having normal or controlled release characteristics can be obtained in accordance with the invention.

In a preferred method according to the invention morphine sulphate, or other water soluble drug, e.g. tramadol, is used in an amount which results in particles containing e.g. between <1% and 90%, especially between about 45% and about 85% e.g. 75 w/w active ingredient for a high dose product and e.g. <1 and 45% for a low dose product.

In the method of the invention preferably all the drug is added in step (a) together with a major portion of the hydrophobic or hydrophilic fusible carrier or diluent used. Preferably the amount of fusible carrier or diluent added in step (a) is between e.g. 10% and <99% w/w of the total amount of ingredients added in the entire manufacturing operation.

In step (c) the amount of optional additional fusible carrier or diluent added is preferably between 5% and 75% w/w of the total amount of ingredients added. The additional material may be added stepwise.

Stage (a) of the process may be carried out in conventional high-shear mixers with a standard stainless steel interior, e.g. a Collette Vactron 75 or equivalent mixer. The mixture is processed until a bed temperature above 40°C is achieved and the resulting mixture acquires a cohesive granular texture, with particle sizes ranging from about 1-3mm to fine powder in the case of non-aggregated original material. Such material, in the case of the embodiments described below, has the appearance of agglomerates which upon cooling below 40°C have structural integrity and resistance to crushing between the fingers. At this stage the agglomerates are of an irregular size, shape and appearance. The resulting mass is then extruded as described above.

In one preferred form of the process of the invention processing of the extruded materials is continued, until the hydrophobic and/or hydrophilic fusible carrier or diluent materials used begin to soften or melt and additional hydrophobic and/or hydrophilic fusible carrier or diluent material is then added. Mixing is continued until the mixture has been transformed into particles of the desired predetermined size range.

In order to ensure uniform energy input into the ingredients in the high speed mixer it is preferred to supply at least part of the energy by means of microwave energy.

Energy may also be delivered through other means such as by a heating jacket or via the mixer impeller and chopper blades.

After the particles have been formed they are sieved to remove any over or undersized material and then cooled or allowed to cool.

The resulting particles may be used to prepare dosage units e.g. tablets or capsules in manners known per se.

We have found that by suitable selection of the materials used in forming the particles and in the tabletting and the proportions in which they are used, enables a significant degree of control in the ultimate dissolution and release rates of the active ingredients from the compressed tablets.

Suitable substances for use as hydrophobic carrier or diluent materials are natural or synthetic waxes or oils, for example hydrogenated vegetable oil, hydrogenated castor oil, beeswax, carnauba wax, microcrystalline wax and glycerol monostearate, and suitably have melting points of from 35 to 150°C, preferably 45 to 90°C.

Suitable substances for use as hydrophillic carrier or diluent are Polyethylene glycols (PEGs) of various molecular weights e.g. 1,000 to 20,000, preferably 4,000 to 10,000.

The optionally added release control component when a water soluble, fusible material may be a PEG of appropriate molecular weight; suitable particulate inorganic and organic materials are dicalcium phosphate, colloidal anhydrous silica, calcium sulphate, talc, lactose, poloxamers, microcrystalline cellulose, starch, hydroxy propylcellulose, hydroxy propylmethyl cellulose.

In this process of the invention the temperature of the mixing bowl throughout the mechanical working is chosen so as to avoid excessive adhesion, suitably to minimise adhesion of the material to the walls of the bowl. To minimise adhesion we have generally found that the temperature should be neither too high nor too low with respect to the melting temperature of the material and it can be readily optimised to avoid the problems mentioned above. For example in the processes described below in the Examples a bowl temperature of approximately 50 - 60°C has been found to be satisfactory and avoids adhesion to the bowl. It is not possible to generalise as to the appropriate temperature or period for the mechanical working for any particular mixture to be processed. However, in practice, it is a matter of simple experimentation and observations to establish a suitable temperature and processing time for a particular mixture under consideration.

To produce tablets in accordance with the invention, particles produced as described above may be mixed or blended with the desired excipient(s), if any, using conventional procedures e.g. using a Y-Cone or bin-blender and the resulting mixture compressed according to conventional tabletting procedure using a suitably sized tabletting tooling. Tablets can be produced using conventional tabletting machines, and in the embodiments described below

were produced on standards single punch F3 Manesty machine or Kilian RLE15 rotary tablet machine.

Generally speaking we find that even with highly water soluble active agents such as salts of morphine or tramadol, tablets formed by compression according to standard methods give very low in vitro release rates of the active ingredient e.g. corresponding to release over a period of greater than 24 hours, say more than 36. We have found that the in vitro release profile can be adjusted in a number of ways. For instance in the case of water soluble drugs a higher loading of the drug will be associated with increased release rates; the use of larger proportions of the water soluble fusible material in the particles or surface active agent in the tabletting formulation will also be associated with a higher release rate of the active ingredient: Thus, by controlling the relative amounts of these ingredients it is possible to adjust the release profile of the active ingredient, whether this be water soluble or water insoluble.

In order that the invention may be well understood the following examples are given by way of illustration only.

EXAMPLE

700g of finely powdered morphine sulphate and 220g of finely powdered hydrogenated vegetable oil were placed in the bowl of a 10 litre capacity Collette Vactron Mixer (or equivalent) equipped with variable speed mixing and granulating blades. The ingredients

were mixed at about 425 rpm with the jacket temperature at 55°C to 65°C, until the contents of the bowl are agglomerated.

The mass is extruded through 1mm holes of an Alexanderwerk extruder equipped with a cutting blade located so as to cut the extrudate into approximately 1.0mm length pieces.

The short lengths of extrudate are collected and returned to the warm bowl of the mixer and operation of the mixture is recommenced. After the extrudates become generally rounded, a further 80 gm of finely divided hydrogenated vegetable oil is added to the bowl and mixing is continued for 3 minutes when the extrudates are generally spherical.

The spherical particles are removed from the bowl, allowed to cool and are then sieved to isolate the sieve fraction 0.5 to 2.0mm.

The release rates of the sieved particles are then assessed by modified Ph. Eur. Basket method at 100 rpm in 900 ml aqueous buffer (ph 6.5) containing 0.05% w/w polysorbate 80 at 37°C and the results are given below:-

TABLE

HOURS AFTER START OF TEST	% OF MORPHINE SULPHATE RELEASED
1	6
2	11
4	21
8	37
12	48
16	57
24	67
30	72

CLAIMS

1. A process for the manufacture of particles, preferably sustained release particles, which comprises

(a) mechanically working in a high-shear mixer, a mixture of a particulate drug and a particulate, hydrophobic and/or hydrophilic fusible carrier or diluent having a melting point from 35 to 150°C and optionally a release control component comprising a water-soluble fusible material or a particulate, soluble or insoluble organic or inorganic material, at a speed and energy input which allows the carrier or diluent to melt or soften whereby it forms agglomerates; and

(b) extruding the resulting material.

2. A process according to claim 1, wherein in step (b) the resulting material from step (a) is extruded through a plurality of orifices and is then formed into pieces.

3. A process according to claim 2, which further comprises.

(c) continuing mechanically working the pieces of extrudate optionally with the addition of a low percentage of the carrier or diluent; and optionally

(d) repeating steps (c) and possibly (b) one or more times

4. A process according to any one of claim 1 to 3, wherein during the mechanical working, heat is supplied thereto by microwave radiation.

5. A process according to claim 4, wherein only part of the heating is supplied by microwave radiation.

6. A process according to any one of claims 1 to 5, wherein the drug is morphine tramadol, hydromorphone, oxycodone, diamorphine or a pharmaceutically acceptable salt of any one of these.

7. A process according to any one of claims 1 to 6, wherein the hydrophobic fusible carriers(s) or diluent(s) is a wax, e.g. chosen from hydrogenated vegetable oil, hydrogenated castor oil, Beeswax, Carnauba wax, microcrystalline wax and glycerol monostearate.

8. A process according to any one of claims 1 to 7, wherein the hydrophilic fusible material optionally included in the mixture in step (a) is PEG having a molecular weight of from 1,000 to 20,000, or a poloxamer.

9. A process according to any one of claims 3 to 8 wherein the fusible carrier or diluent is added stepwise during mechanical working during step (c).

10. A solid dosage form obtainable by compressing particles obtained by the process of any one of claims 1 to 9 form optionally containing conventional tabletting excipients.

11. A capsule for oral dosing containing particles obtained by the process of any one of claims 1 to 9 and optionally containing conventional capsuling excipients.

12. A solid dosage form as set forth in claim 10 or 11, wherein the active ingredient is unstable in water.

INTERNATIONAL SEARCH REPORT

Inv onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 204 596 (RHONE POULENC SANTE) 10 December 1986 see claims 1,3 see column 3, line 43 - column 4, line 21 see example 1	1,7,10, 11
X	EP,A,0 465 338 (RHONE POULENC NUTRITION) 8 January 1992 see claims 1,2,4 see page 3, line 13 - line 15	1,7,10, 11
P,X	EP,A,0 624 366 (EUROCELTIQUE) 17 November 1994 see the whole document	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Information on patent family members

Int ional Application No
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-204596	10-12-86	FR-A-	2581541	14-11-86
		AU-B-	579012	10-11-88
		AU-B-	5722486	13-11-86
		CA-A-	1266841	20-03-90
		JP-A-	61260029	18-11-86
EP-A-465338	08-01-92	FR-A-	2663818	03-01-92
		AU-B-	643037	04-11-93
		AU-B-	7939591	02-01-92
		CA-A-	2045883	30-12-91
		HU-B-	208785	28-01-94
		JP-A-	4230318	19-08-92
		RU-C-	2035164	20-05-95
		US-A-	5290560	01-03-94
EP-A-624366	17-11-94	DE-A-	4315525	17-11-94
		GB-A-	2284760	21-06-95
		GB-A-	2287880	04-10-95
		AU-B-	6196394	17-11-94
		CA-A-	2123160	11-11-94
		CN-A-	1099262	01-03-95
		CZ-A-	9401093	16-11-94
		FI-A-	942092	11-11-94
		JP-A-	7053361	28-02-95
		NO-A-	941719	11-11-94
		AU-B-	6610594	12-01-95
		AU-B-	7901594	01-06-95
		BG-A-	99077	30-06-95
		BG-A-	99078	28-07-95
		CA-A-	2127166	02-01-95
		CZ-A-	9401550	18-01-95
		CZ-A-	9402866	14-06-95
		EP-A-	0636370	01-02-95
		EP-A-	0654263	24-05-95
		FI-A-	943141	02-01-95
		FI-A-	945476	24-05-95
		JP-A-	7149648	13-06-95
		JP-A-	7196475	01-08-95
		NO-A-	942470	02-01-95
		NO-A-	944473	24-05-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inv onal Application No
PCT/GB 95/02579

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-624366		PL-A-	304062	09-01-95
		PL-A-	305939	29-05-95
		AU-B-	1475595	21-09-95
		CA-A-	2144500	15-09-95
		CN-A-	1102323	10-05-95
		EP-A-	0672416	20-09-95
		FI-A-	951155	15-09-95
		NO-A-	950950	15-09-95